Alberta Heritage Foundation
for Medical Research

Functional diagnostic imaging in the assessment of myocardial viability

Part 1 - Overview

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This Health Technology Assessment Report has been prepared on the basis of available information of which the Foundation is aware from public literature and expert opinion and attempts to be current to the date of publication. It has been externally reviewed. Additional information and comments relative to the Report are welcome and should be sent to:

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Summary

- The assessment of viability in dysfunctional myocardium has important clinical implications. If sufficient viable tissue is present, revascularization may result in improved left ventricular function, improved quality of life and longer survival. If it is not present, there may be no recovery of function.
- Imaging techniques used to assess myocardial viability include single photon emission computed tomography (SPECT), positron emission tomography (PET), dobutamine echocardiography (DEC) and magnetic resonance imaging (MRI).
- These imaging methods have the potential to improve the management of patients with dysfunctional myocardium and to lead to efficiencies through avoidance of inappropriate procedures in those with symptoms of heart failure who would not benefit from revascularisation.
- However, review of the available literature suggests that the place of these technologies in routine health care is still uncertain. There are substantial methodological limitations in most reported studies. There are few good quality data on their influence on patient management decisions.
- PET and DEC seem to have similar levels of accuracy in this application, though the evidence is limited.
- There is some evidence that PET is able to predict outcomes, but this is not conclusive. The evidence for the predictive value of DEC is very limited.
- There is some evidence that Tl-201 SPECT could have higher sensitivity but lower specificity than PET. However, studies which found higher specificities for Tl-201 SPECT were of poorer quality.
- Outcomes studies suggest that Tl-201 SPECT examinations may have a useful predictive value, but their reliability is uncertain.
- FDG SPECT appears to have comparable sensitivity to PET and DEC, but the studies undertaken so far are methodologically weak and tend to overestimate its accuracy. Sestamibi SPECT appears to be less accurate than PET or Tl-201 SPECT.
- The feasibility of imaging FDG uptake with SPECT has been demonstrated but the quality of the available evidence does not allow an adequate evaluation of its potential role in routine clinical practice.
- The role of SPECT imaging with Tc-99m-labeled agents is not yet determined.
- There is still limited evidence on MRI methods, but there are indications that these may become more important in the future.

- There is limited evidence for improvements in outcome after revascularization for patients who have been selected for such intervention on the basis of imaging examinations.
- The promise of these imaging techniques is not yet matched by convincing evidence of benefit to health care. Data on comparative performance are limited and technical development continues to be rapid.
- Any use in Alberta of these methods for assessment of myocardial viability should be associated with prospective studies involving long term follow up of patients.

Glossary

Asynergia (akinesia) - lack of coordination among parts or organs normally acting in harmony

Coronary angiography – radiographic visualization of coronary arteries after the introduction of contrast material

Diastole – period of relaxation of heart muscle with chamber filling

Dyssynergia (dyskinesia) – disturbance of muscular coordination

Endocardium – the thin endothelial lining of the cavities of the heart and the connective tissue bed on which it lies

Hypokinesia – abnormally decreased mobility; abnormally decreased motor function or activity

Hypoxia – a low tissue oxygen tension due to low blood saturation or low flow

Ischemia – deficiency of blood in a part, usually due to functional constriction or actual obstruction of a blood vessel

Inotropic – affecting the force or energy of muscular contractions

Infarct - an area of coagulation necrosis in a tissue due to local ischemia resulting from obstruction of circulation to the area, most commonly by a thrombus or embolus

Infarction - the formation of an infarct; an infarct

Mitochondria - small organelles within the cytoplasm that function in cellular metabolism and respiration; they provide the principal source of celullar energy through oxidative phosphorylation and adenosine triphosphate (ATP) synthesis.

Myocardial infarction - necrosis of the myocardium as a result of interruption of the blood supply to the area

Myocardial ischemia – deficiency of blood supply to the myocardium adjacent to the endocardium

Myocardial hibernation – chronic but potentially reversible cardiac dysfunction caused by chronic myocardial ischemia, persisting at least until blood flow is restored

Myocardial perfusion scintigraphy – use of scintigraphy to assess regional myocardial blood flow and cell viability

Myocardial stunning – temporary impairment of contraction following prolonged ischemia, lasting hours or days, and occurring despite a normal blood supply

Myocardium – the middle and thickest layer of the heart wall, composed of cardiac muscle

Necrosis - the sum of the morphological changes indicative of cell death and caused by progressive degradative action of enzymes; it may affect groups of cells or part of a structure or an organ

Perioperative – pertaining to the period extending from the time of hospitalization for surgery to the time of discharge

Phosphorylation - the metabolic process of introducing a phosphate group into an organic molecule

Sarcolemma - a membrane that covers smooth, striated and cardiac muscle fibres

Scintigraphy – use of a scintillation camera to obtain 2D images of the distribution of radioactivity in tissues after the administration of a radioactive tracer

Stenosis - narrowing or stricture of a duct of canal

Stunning - loss of function, analogous to unconsciousness

Systole – the period of heart muscle contraction resulting in a rise of pressure and ejection of blood

Transmural – through the wall of an organ; usually applied to ischemia or infarction extending through or affecting the full thickness of the left ventricular wall

Ventriculography - radiography of a ventricle of the heart following introduction of contrast medium

Sources: Dorland's Illustrated Medical Dictionary (28th edition).
Mosby's Medical, Nursing, & Allied Health Dictionary (4th edition).
Dr. I. McDonald (personal communication)

Abbreviations

CABG – coronary artery bypass grafting

CAD – coronary artery disease

CI - confidence interval

DEC – dobutamine echocardiography

DM – diabetes mellitus

Echo - echocardiography

FDG – fluorine-18 (^{18}F-labeled) fluorodeoxyglucose

FDI – functional diagnostic imaging

fMRI – functional magnetic resonance imaging

HE – high energy

LDDE – low dose dobutamine echocardiography

LEHR – low-energy high-resolution

LE - low energy

LV – left ventricular

LVD - left ventricular dysfunction

LVEF – left ventricular ejection fraction

LVF - left ventricular function

MI - myocardial infarction

MRS – magnetic resonance spectroscopy

MV - myocardial viability

MVD - multivessel disease

NA – not available

NPV –negative predictive value

PET – positron emission tomography

PPV – positive predictive value

prev. - previous

pts – patients

PTCA – percutaneous transluminal coronary angioplasty

Rb-82 – rubidium-82

Revasc – revascularization

ROC – receiver operating characteristics

RWM – regional wall motion

SPECT – single photon emission tomography

Se - sensitivity

Segs - segments

Sp – specificity

SS – statistically significant(ly)

Tc-99m MIBI – technetium 99m sestamibi

Tl-201 – thallium-201

vs. – versus

WM – wall motion

Introduction

This report has been prepared in view of the continuing interest in positron emission tomography and other functional diagnostic imaging (FDI) methods within the Alberta health care system. It also continues the work at the Alberta Heritage Foundation for Medical Research in developing approaches to assessment of diagnostic imaging technologies.

A number of techniques have been applied to the imaging of the myocardium. The focus of this report is on their application to the assessment of myocardial viability (MV) in patients with chronic heart disease, who are being considered for revascularization. It does not cover their use in the detection of heart disease or the assessment of viability in patients after acute myocardial infarction.

A detailed review of the literature has been undertaken for single photon emission computed tomography (SPECT) using thallium - 201 or fluorodeoxyglucose (FDG), positron emission tomography (PET), and dobutamine echocardiography (DEC). In addition, an appraisal of reviews dealing with SPECT with technetium - 99m (Tc-99m) - labelled agents, and a short overview of magnetic resonance methods have been included. Details of the methodology used are included in Appendix A.

Because of the considerable amount of detail in this analysis, the report has been prepared in two parts. This volume gives an overview of the assessment findings and some discussion on the place of the FDI techniques in the application under consideration. Part 2 contains the full results of the literature review.

Approaches to the assessment of myocardial viability

Techniques for the assessment of viability in dysfunctional myocardium fall into four broad categories (62):

- detection of active metabolism, using FDG as a marker of glucose uptake, or tracers of oxidative metabolism such as C-11 acetate, and imaging with PET or high energy SPECT;
- identification of contractile reserve using functional echocardiography or magnetic resonance imaging;
- studies of perfusion, for example with N-13 ammonia and PET, or myocardial contrast echocardiography; and
- assessment of cell membrane integrity using thallium-201 and SPECT or planar gamma camera imaging.

Patients who have survived coronary occlusion, or who have severe coronary artery disease, can suffer from left ventricular dysfunction (LVD), a condition in

which the left ventricle of the heart has reduced capacity to contract. Severe LVD can result in heart failure symptoms, reduced quality of life and a high mortality rate.

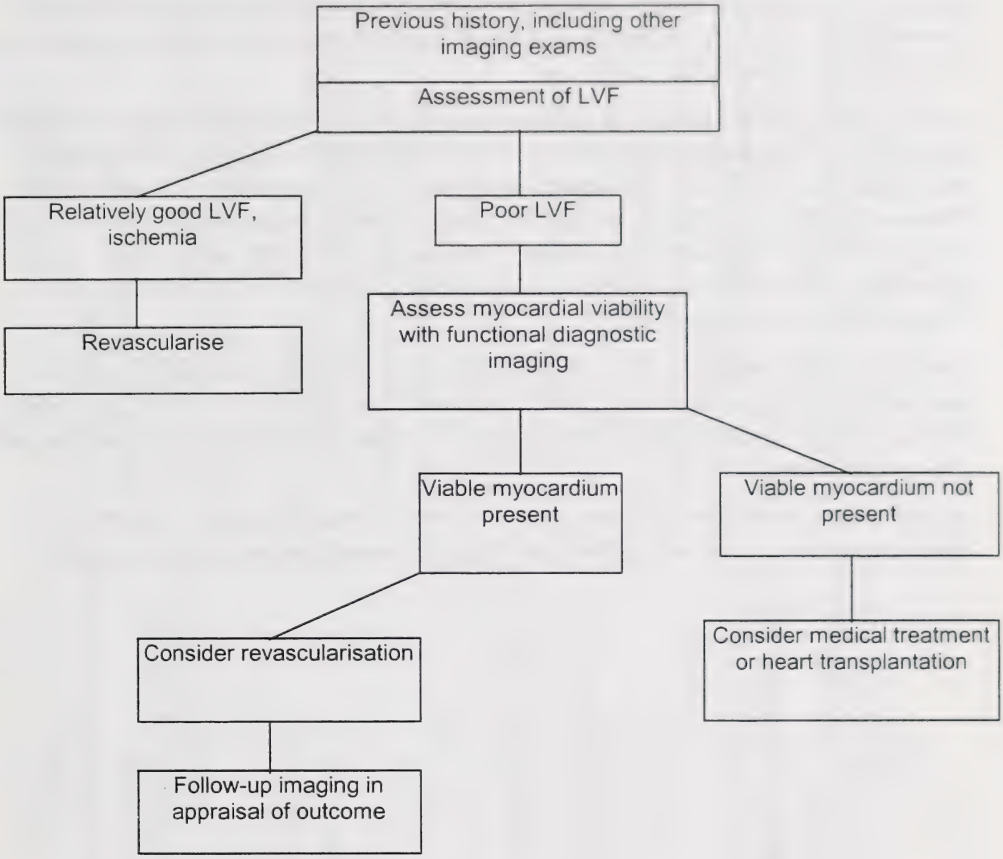
If the loss of contractile function is due to the death of myocardial tissue (infarction) it is irreversible. Myocardium can also lose contractile function as a result of chronically inadequate or repeatedly interrupted blood supply, but remain viable. It can recover function when adequate blood supply is restored. The term "hibernating myocardium" is often used for myocardial regions in this state (62).

The assessment of viability in dysfunctional myocardium has important clinical implications (17). If sufficient viable tissue is present, revascularization may result in improved left ventricular function (LVF), improved quality of life and longer survival. If it is not present, there may be no recovery of function.

For patients with relatively good left ventricular function and evidence of ischemia, revascularization may be indicated in any case (17). For patients with poor left ventricular function (ejection fraction 35% or less), revascularization carries an increased risk of complications and may be ineffective if viable tissue is not present. It is argued that for these patients, viability studies are indicated (17).

Assessment of MV with FDI techniques considered in this report has therefore been proposed for a comparatively small group of patients - those whose primary clinical problem is heart failure symptoms - rather than for all those who have a dysfunctional myocardium. The other therapeutic options for these patients are medical therapy and heart transplantation. It has been suggested that viability studies can result in some patients being referred for revascularization instead of heart transplantation (62). A generalised approach to using FDI methods in this application is shown in Figure 1.

Figure 1: Use of diagnostic imaging in the assessment of myocardial viability



LVF - left ventricular function

Revascularization may be achieved by coronary artery bypass surgery (CABG) or coronary angioplasty (PTCA). For patients with poor ventricular function, reported mortality rates for CABG range from 5% to 37% (62). PTCA is a much safer procedure but is limited to suitable coronary artery lesions and restenosis occurs in a high proportion of cases.

Earlier studies had provided evidence of the benefits of revascularization in prolonging survival. In the 1970s, studies of contractile reserve involved the use of a chemical stimulant, epinephrine, or an electrophysiological technique, postextrasystolic potentiation, during contrast ventriculography (70). In 1982, a study was published of five-year survival rates of patients, with left ventricular ejection fractions less than 50%, who were tested in this way. It showed that in comparison with patients with no contractile reserve, survival rates for patients

with contractile reserve were significantly higher, whether surgically or medically treated. Left ventricular ejection fraction and symptomatic state improved more after surgery for these patients. These findings supported the concept that coronary revascularization enhances function of dysfunctional but viable myocardium (70).

Yusuf et al. (110) undertook a systematic review of seven randomized controlled trials (RCTs) that had compared outcomes of CABG (n = 1,324) and medical management (n = 1,325) for patients with stable coronary artery disease (CAD). Those who received CABG had significantly lower mortality at five, seven and ten years following the intervention. The benefits of CABG were most pronounced for individuals in the highest risk categories, such as those with lower LVEF and abnormal LVF.

Data from the Coronary Artery Surgery Study (CASS) Registry (67) for 8,221 patients who had a first time CABG indicated that 90% were alive at five years, 74% at ten years and 56% at fifteen years. Survival exceeded that of the matched U.S. population.

Information of this sort points to the need for MV studies which may help in identifying those who would be most likely to benefit from revasularization.

Table 1: Comparison of cardiac FDI techniques

Technology	Basis of data	Main Advantages	Main limitations
FDG PET	*detects changes in energy metabolism	*high resolution and good spatial localization of defects *possibility for attenuation correction *data can be analyzed qualitatively and quantitatively *can be applied to measure various abnormalities (using different tracers)	*minimally invasive *high overall technical cost *limited availability *does not have capabilities of displaying anatomy *need for a cyclotron; FDG is expensive
FDG SPECT	*detects changes in energy metabolism	*lower overall technical cost than for PET *widely available SPECT equipment	*minimally invasive *need for cyclotron for FDG production; FDG is expensive *Poorer spatial resolution than PET; lower sensitivity than PET *requires specialized equipment and staff *requires attenuation correction technique
MRS	*detects metabolic changes	*non-invasive *offers possibility of in vivo measurement of myocardial biochemistry can be performed with available MRI equipment *3-D capability with unlimited field of view	*limited spatial resolution *time consuming *patients with ferromagnetic objects in their bodies must be excluded *requires specialized software and expertise *evaluation is limited to the anterior wall of myocardium *abnormalities of PCr and ATP are not specific for ischemia or absence of viability
FMRI	*measures contractile reserve (thickness & WM)	*can be performed on available MRI scanners (permits direct correlation of function with the underlying anatomy) *does not use ionizing radiation *good spatial resolution of LV cavity and wall thickness in diastole and systole	*patients with ferromagnetic objects in their bodies must be excluded *relatively long scanning time *relatively high costs of additional equipment, software

Table 1: Comparison of cardiac FDI techniques (cont'd)

Technology	Basis of data	Main Advantages	Main limitations
Echo-cardiography	*measures contractile reserve (thickness & WM)	*versatile imaging method for a variety of heart diseases *all cardiac structures visualized and pump function assessed *relative low-cost; no needles or radiation; easy portable *does not depend on ECG-gating (rhythm) *good resolution of LV wall thickness during cardiac cycle	*dependent on operator's skill to acquire images and requires specialized equipment and experienced interpreters (especially stress echo) *stress echo cannot evaluate myocardial perfusion adequately on a routine basis *uncertain definition of LV cavity size
Tc-SPECT	*measures myocardial perfusion and membrane integrity	*lower overall technical cost than for PET *widely available SPECT equipment *Tc-99m sestamibi has better radiation characteristics than Tl-201 *time of Tc-99m sestamibi imaging is not critical (minimal redistribution)	*minimally invasive *the utility of Tc-99m sestamibi alone as an indicator of MV is limited (reduced value as MV agent under ischemic and hypoxic conditions) *requires adequate attenuation correction technique
Tl-201 SPECT	*measures myocardial perfusion and membrane integrity	*lower overall technical cost than for PET *widely available SPECT equipment *provide assessment of presence and extent of CAD as well as MV	*minimally invasive (requires radioisotope injection) *uptake depends on blood flow, extraction efficiency, retention by viable myocytes *redistribution & uptake depend on time after injection and its blood concentration *suboptimal radiation characteristics

LV - left ventricular viability WM - wall motion PCr - phosphocreatine ATP - adenosine triphosphate MV - myocardial

Positron emission tomography in the assessment of myocardial viability

Background

Positron emission tomography (PET) has been a research tool for many years, but over the past decade has increasingly been applied in routine clinical care.

In 1986, Tillisch et al (98) reported that PET could identify viable myocardium in dysfunctional regions of the left ventricle with a relatively high degree of accuracy. The techniques used involved the identification of regions where there was a mismatch between glucose utilization (measured by FDG uptake) and blood flow (measured using N-13 ammonia). In normal myocardium, fatty acids are the primary substrate for energy metabolism, but in ischemic myocardium there is a shift from aerobic to anaerobid metabolism, and glucose becomes the preferred substrate. Increased FDG uptake in regions of reduced perfusion indicates reversibly injured myocardium.

A difficulty with the mismatch technique is that N-13 is a short-lived isotope and a cyclotron on-site would be required for its production. Alternative approaches to PET include the use of generator-produced rubidium-82 for perfusion studies and assessment of viability through the measurement of FDG uptake alone. There have also been studies of the use of C-11 acetate for the detection of viability.

Since 1986, a number of studies of the accuracy of PET in identifying viable myocardium have been reported. In most cases, accuracy was measured, as in the paper by Tillisch et al. (98), on the basis of segment function. Images of the left ventricle were divided into segments for image analysis. Dysfunctional myocardial segments with mismatch were predicted to recover function on revascularization.

The reference method or gold standard used in these segmental studies was analysis of wall thickening and motion before and after revascularization, by contrast or radionuclide angiography (ventriculography), or by echocardiography. Viable segments were defined as those with improved function after revascularization.

In some studies, accuracy was calculated in a clinically more relevant way, on a patient basis. In these studies viability was defined on the basis of improved segmental function, and/or improvement in the function of the entire left ventricle, measured for example by LVEF.

Accuracy of PET in the identification of viable myocardium

Seventeen papers were identified which addressed the accuracy of PET in identifying viable regions in dysfunctional myocardium. They included the twelve studies identified in a recent review by Bax et al. (20). For two studies (30, 96), it was considered that sensitivity and specificity could not be calculated with validity. A more recent paper (107) provides positive and negative predictive values, but does not include data that would allow the calculation of sensitivity and specificity.

In 12 papers, accuracy was calculated on a segmental basis. In some cases it was based on all dysfunctional segments, while in others only segments shown to be revascularized were taken into account. In two papers, accuracy calculations were patient-based. In one paper, accuracy data were provided for both segments and patients.

Table 2 summarizes the results of the papers in which accuracy calculations were based on segmental analysis. Results varied substantially. Sensitivity values ranged from 71 to 99%, and specificity from 33 to 86%.

Three patient-based analyses (7, 43, 59) gave sensitivities of 82 to 96% and specificity from 69 to 91%. The number of patients in each study was quite small and the accuracy values would have wide confidence intervals.

Only three papers published since 1992 on the accuracy of C-11 acetate in the detection of viable myocardium were identified. From two of these (44, 107), PPVs for C-11 PET were 67% and 79%, compared to 52% and 78% for FDG PET. NPVs were 89% and 90% for C-11 PET and 85% for FDG.

Table 2: Results of studies on the accuracy of FDG PET in predicting recovery of myocardial function after revascularization – segment-based analysis.

Paper	Sensitivity	Specificity	Predictive values (where provided)
Tillisch et al. 1986 (98)	95%	80%	PPV 85%, NPV 92%
Tamaki et al. 1989 (96)	78%	78%	
Marwick et al. 1992 (63,63)	71%	76%	
Lucignani et al. 1992 (57)	93%	86%	
Gropler et al. 1993 (44)	83%	50%	
Knuuti et al. 1993 (53)	85%	84%	
Paolini et al. 1994 (75)	88%	79%	
Tamaki et al. 1995 (93)	88%	82%	PPV 76% NPV 92%
Gerber et al. 1996 (41)	75%	67%	
Baer et al. 1996 (7)	93%	66%	
Vom Dahl et al. 1996 (105)	92%	35%	PPV 61% NPV 80%
Wolpers et al. 1997 (107)			PPV 78% NPV 85% (Glucose utilization)
Pagano et al. 1998 (72)	99%	33%	

Appraisal of papers on PET accuracy

These papers were appraised according to the criteria listed in Appendix A. None of the papers met all the appraisal criteria.

Only six of the 17 studies (35%) were clearly prospective in design, and in only three of these was there adequate evidence of unbiased patient selection (consecutive patients in these cases). Consecutive patients were selected in only five of the 11 retrospective studies, giving a total of eight studies based on consecutive patients (47%). The study group matched the target population well in five studies (29%). Interpreters of PET were blind to clinical data and results of other tests in only two cases (12%) while the interpreters of post-operative ventricular function tests were blind to the results of PET in ten studies (59%).

A major problem in some studies was post-test selection bias, which could seriously influence results. If the papers with clear evidence of such bias are excluded, the ranges for reported sensitivity and specificity of segment-based FDG accuracy studies become 71-95% and 66-86% respectively. Ranges for patient-based studies are unaffected.

Overall, the quality of the PET accuracy studies is limited. They provide only limited evidence for the accuracy of PET in this application.

Contribution of PET myocardial viability studies to patient management and outcome

Seven comparative studies (37, 39, 56, 73, 94, 104, 109) were identified which addressed the issue of outcomes for patients who have undergone PET myocardial viability studies. All but one (104) appeared to be retrospective, with no evidence that patient selection was blinded to outcomes, although in most cases it appears that consecutive patients were chosen. The study population matched the target population (those with LVEF 35% or less) well in only three studies (37, 39, 73). Brief details are shown in Table 3.

Two observational studies of outcomes were found (75, 97). Paolini et al. (75) followed up 17 patients who were assessed for CABG on the basis of PET studies, for an average 28 months. Nine patients with PET mismatch underwent CABG. There were no deaths in this group and for seven patients, clinical status improved. There were two deaths in the group who did not undergo CABG, and for three other patients, clinical status worsened.

Tan et al. (97) followed up 33 patients who were assigned to revascularization or medical treatment on the basis of PET viability findings. In the group with positive viability results, 14 underwent CABG and five had PTCA. The mortality rate was 10.5%. There was a significant improvement in LVEF and heart failure symptoms after revascularization. In the medically-treated group, the mortality rate was 14% and there was a smaller improvement in symptoms.

One study has examined the impact of PET myocardial viability assessments on clinical decision making. Beanlands et al. (21) used a questionnaire to physicians before and after PET studies to measure the influence of PET on management choices. They found that the PET studies influenced management choices in 57% of all cases, and in 71% of those where the patient had a left ventricular ejection fraction of less than 30%.

In summary, there is some evidence that PET viability studies predict improved outcomes after revascularization. However, because of problems such as short follow-up periods, the possibility of selection bias, and small sample size, the evidence to date cannot be considered conclusive.

Table 3 PET myocardial viability comparative outcomes studies: patients and results

Study	No and age of patients	Follow-up period	Groups compared	Outcomes evaluated	Results
Eitzman et al. 1992 (39)	82 59y±10	Average 12 months	PET mismatch: *revascularized (26); medical treatment(18).* *No mismatch:* revascularized (24); medical treatment (24).	Major cardiac events (death, AMI, cardiac arrest, late revascularization)	Significantly higher number of events in medically treated mismatch group than other groups.
Yoshida, Gould 1993 (109)	35 54y (36-80)	3 ±0.3 years	*PET mismatch*: revascularized (20); medical treatment(5). *No mismatch*: revascularized (4); medical treatment(6).	Death	Differences in mortality between groups not statistically significant. Significantly lower mortality for mismatch patients than others.
Tamaki et al. (94)	84 58y±9	23±12.7 months	PET viable, medically treated (48); PET nonviable, medically treated (36).	Major cardiac events (death, nonfatal myocardial infarction, unstable angina, late revascularization)	Increased FDG uptake (indicating viability) strongest predictor of future event
Di Carli et al. 1994 (37)	93 65y±10	Average 13.6 months .	*PET mismatch:* revascularized, (26); Medical treatment (17). *No mismatch:* revascularized (17); medical treatment (33).	Survival, changes in angina, symptoms of heart failure	Annual survival probability : *For mismatch* revascularized 88%, medical 50% *For no mismatch* Revascularized 94% medical 92% Significant improvement in heart failure symptoms only for revascularized mismatch patients.

Table 3 PET myocardial viability comparative outcomes studies: patients and results (cont'd)

Study	No and age of patients	Follow-up period	Groups compared	Outcomes evaluated	Results
Lee et al. 1994 (56)	129 62y±11	17±9 months	*PET mismatch*: revascularized (49); medical treatment (21). *No mismatch:* revascularized (19) medical treatment (40).	Major cardiac events – death, nonfatal ischemic events (unstable angina, myocardial infarction)	Deaths: distributed evenly across groups Nonfatal ischemic events: higher in medical mismatch than revascularized mismatch group
Vom Dahl et al. 1997 (104)	161 57y±9	29±6 months from recruitment	Medically treated with: scar (63); mild match (5); mismatch (9). Vascularized with: scar (27); mild match (21); mismatch (36).	Major cardiac events – death, myocardial infarction, unstable angina, heart transplant, survived resuscitation. Changes in symptoms.	Cardiac events lower in revascularized mismatch group than medical mismatch or scar groups (statistical significance not demonstrated). Significant improvement in heart failure, angina for vascularized mismatch group compared to medical mismatch
Pagano et al. (72)	35 45-72 y	6 months after CABG.	All underwent CABG.	Changes in LVEF, changes in exercise capacity, quality of life.	Linear correlation between number of viable segments and improvement in LVEF. No correlation with changes in exercise capacity or quality of life.

Dobutamine echocardiography in the assessment of myocardial viability

Background

It has been shown that dysfunctional but viable myocardium has a contractile reserve that can be activated by inotropic stimulation (62). An inotropic stimulus is one that increases the force of muscular contraction.

Echocardiography has been used in the detection of viability through the identification of contractile reserve. In comparison with PET, echocardiography has a lower cost and is more accessible. It can be used at the patient's bedside. On the other hand, the technique requires sophisticated digital processing and a high level of expertise. In addition, for some patients, it is difficult to obtain echocardiograms of diagnostic quality (102). An important recent development has been the use of 'harmonic imaging'. This has the effect of increasing the signal to noise ratio of the image, picking up weaker endocardial signals and visualizing walls not otherwise visible. This has extended the scope of stress echocardiography (McDonald, personal communication).

Most commonly, dobutamine is the inotropic stimulant used. Contractile reserve is usually identified by improvements in left ventricular wall motion and thickening in response to low doses of dobutamine.

Effects of dobutamine may vary according to the dose. Myocardial segments which improve in function at a low dose (10μg/kg/min) may deteriorate at a high dose (40μg/kg/min). This biphasic response has been suggested as an accurate indicator of viability. However, high doses of dobutamine are associated with significant adverse effects. In two studies using high dose dobutamine, angina occurred in most patients (4, 33). Even at low doses there can be adverse effects in some patients, such as ventricular arrhythmias (76, 77, 88).

Other echocardiographic techniques for the detection of myocardial viability have been investigated. They include the use of dipyridamole or postextrasystolic potentiation as the inotropic stimulus, and myocardial contrast echocardiography.

Accuracy studies

Some 29 papers dealing with the accuracy of dobutamine echocardiography (DEC) were identified. Some of these were not primarily concerned with the accuracy of the technique but were principally comparative studies or studies of particular types of patients. They were included in this assessment if accuracy measures were presented or extractable from the published data.

Of these 29 papers, 21 presented segment-based analyses only, six included both segment-based and patient-based analyses, and two were patient-based only. Details of these papers are given in Part 2.

The reference method used was analysis of wall thickening and motion before and after revascularization, by echocardiography. Viable segments were defined as those with improved function after revascularization. For patient-based studies, viability was defined on the basis of improved segmental function, and/or improvement in the function of the entire left ventricle, such as improvement in LVEF.

Ranges for sensitivity and specificity obtained in the different tyes of study are summarised in Table 4. Further details are provided in Volume 2, including consideration of pre-test selection bias.

The results with high-dose dobutamine appear to be good, but the adverse effects of this test need to be taken into account. In addition, confidence intervals would be wide in the patient studies.

Table 4 : Data from accuracy studies with dobutamine echocardiography

Type of study	Sensitivity %	Specificity %
Segmental, low – medium dose	60 – 97	30 - 94
Patient – based, low –medium dose	82 – 100	70 - 88
Segmental, high dose	60 – 87	83 - 90
Patient – based, high dose	80 – 92	81 - 90

As with the papers on accuracy of PET, problems in methodology included study design, selection of patients, matching of patients to the target population, blinding of interpreters of tests, and post-test selection bias.

Only 41% of the studies were clearly prospective in design, and consecutive patients were selected in only 48% of all studies. The study group matched the target population well in only 34%. While the interpreters of dobutamine echocardiography were blind to clinical and other test data in 66% of studies, interpreters of reference method echocardiography were blind to dobutamine echocardiography results in only 41% of studies.

Accuracy studies with other echocardiographic techniques

Picano et al. compared use of very-low dose dipyrimadole (a vasodilator), low dose dobutamine, and a combination of the two, in a segment-based accuracy study of viability. Their results suggest that the combined dipyrimadole-dobutamine technique may be more effective than dobutamine alone. Sensitivity and specificity were 72% and 92% for dobutamine and 94% and 89% for the combined approach. These findings would need to be confirmed by other studies.

Scognamiglo et al. have examined the use of postextrasystolic potentiation (PESP) as the inotropic stimulus in echocardiographic studies (88). Their results suggested that the PESP technique (sensitivity 92%, specificity 86%) may be more accurate than dobutamine echocardiography (sensitivity 86%, specificity 81%). These results would also need confirmation. This technique may be unpleasant for patients, as it involves insertion of an electrode through the nose into the esophagus.

Myocardial contrast echocardiography (MCE) is a technique in which an echocardiographic contrast medium is used to image myocardial perfusion. It has been compared with dobutamine echocardiography for the assessment of myocardial viability in three studies (35, 65 69) which found that while the sensitivity of MCE is comparable to that of dobutamine echocardiography, its specificity is lower.

This technique currently requires cardiac catheterization. It would involve higher costs and perhaps greater risk to patients than dobutamine echocardiography. At this stage there appears to be no evidence to justify its use in this application.

Contribution of DEC myocardial viability studies to patient management and outcome

Two retrospective studies of consecutive patients (3, 106) examined outcomes for patients who had undergone dobutamine echocardiography viability studies.

Williams et al. (106) followed up 108 medically treated patients identified as having myocardial scar, or ischemic or viable tissue, for an average of 16 months after the dobutamine echocardiography study. Major cardiac events were recorded. The event rate was significantly higher in those with viable or ischemic myocardium, independently of LVEF and age. There was no significant difference in event rates between viable and ischemic patients.

Anselmi et al. (3) examined differences in outcome for medically treated and revascularized groups, with or without viability, over an average 16 month follow-up period after therapeutic intervention. The incidence of cardiac death was lower for revascularized patients with viability than for the other groups, but the differences were not statistically significant. For patients with LVEF less than 34%, nonfatal cardiac events were significantly fewer in revascularized patients with viability, and medically treated patients without viability, than the other groups.

Over 50% of the patients in this study had recent myocardial infarction at the time of echocardiography. As well as hibernating myocardium, the study might have identified some stunned myocardium, which can recover spontaneously.

Comparisons of accuracy of PET and DEC

A number of studies have compared the results of PET and dobutamine echocardiography assessments of myocardial viability, without proceeding to measurement of recovery of function after revascularization. In a sense, in these studies, PET was regarded as the gold standard. Given the variability of PET accuracy results, it is not a perfect gold standard, and these studies have very limited value.

Three studies were identified which compared the results of both techniques with recovery of function after revascularization (7, 41, 72). Although these results vary greatly, they consistently indicate that dobutamine echocardiography has a lower sensitivity and a higher specificity than PET.

Ranges for sensitivity and specificity for PET and dobutamine echocardiography, from studies in which revascularization decisions were not influenced by the results with these techniques suggest that echocardiography would be at least comparable to PET in this application.

These echocardiography results have for the most part been obtained at institutions with substantial experience in the technique. It has been suggested that the accuracy of the method will decrease as it becomes more widely utilized by by less experienced observers (102).

To achieve and maintain the level of expertise required for this technique, relatively high throughputs would be required. It would be desirable for these services to be concentrated in relatively few institutions rather than widely dispersed.

Outcome studies based on PET or DEC

The basic argument for performing viability studies is that they will allow selection of patients with viable dysfunctional myocardium who will benefit from revascularization in the following ways:

- survival will be improved for patients with viability if they are revascularized;
- these patients will suffer fewer adverse events if they are revascularized;
- they will experience greater improvement of symptoms if they are revascularized;
- these patients will be at particularly high risk if they are not revascularized;
- patients with no viability will not benefit from revascularization and can be excluded.

Only limited evidence exists for improved survival for patients with viability if they are revascularized, and only in the short term (37). There is more evidence that they will experience fewer adverse cardiac events, and that their symptoms will improve, again in the short term (3, 37, 39, 56, 104). Evidence is conflicting on the question of whether medically treated patients with viable myocardium have poorer outcomes than those who do not. Although there is some evidence of better survival in the long term (70), four papers indicate that in the short term, they may have more adverse cardiac events (39, 56, 94, 106). Most of this evidence has been obtained with groups with less severe ventricular dysfunction than the target population. A summary of findings from outcomes papers is given in Table 5.

Multi-centre studies with larger number of patients matching the target population, and longer follow-up periods would be desirable to confirm the benefits of selection of patients with viable myocardium for revascularization.

Consideration of revascularization for these patients must weigh the evidence of benefits against the risks of the procedure. For CABG, the mortality may be around 10% even at highly experienced institutions. For PTCA, where it can be used, the risk of failure is high. Ultimately, the decision must involve the patient, who should be fully informed of both the risks and the level of evidence for benefit.

Table 5: Summary of findings of outcomes papers

Finding	Number of papers reporting finding
Improved survival for V+ patients if revascularized	1 (37)
Fewer adverse events for V+ patients if revascularized	3 (3, 39, 56)
Improved symptoms for V+ patients if revascularized	2 (37, 104)
Lower survival for medically treated V+ patients in comparison with V- patients.	1(37)
Better survival for medically treated V+ patients in comparison with V- patients.	1(70)
More adverse cardiac events for medically treated V+ patients in comparison with V- patients.	4 (39, 56, 94, 106)
No benefits for revascularized V- patients compared to medically treated V- patients	1 (37)

V+: patients with viable myocardium in dysfunctional regions of the left ventricle.

V- : Patients with no viable myocardium in dysfunctional regions or insufficient to have an effect.

Thallium – 201 scintigraphy in the assessment of myocardial viability

Method

Thallium-201 scintigraphy has been used for many years in the detection and management of coronary artery disease. Diagnostic studies typically involve imaging of the left ventricle with the patient under stress, induced by exercise or pharmaceutical agents, and later imaging with the patient at rest. If there is a region with reduced thallium-201 uptake (a defect) in the stress image, which is reversed in the resting image, the region is considered ischemic but viable. If there is a persistent defect, the region was once considered to be scar tissue. However, as previously noted, PET studies showed that many regions with persistent defects could be viable.

Initial uptake of thallium-201 by myocardial tissue is determined by blood flow. Retention of the radionuclide in the tissue is related to cell membrane integrity, which is maintained only if the tissue is viable (62). A number of studies have investigated delayed imaging with thallium-201 as a technique for identifying viability in dysfunctional regions of the left ventricle.

Two approaches have been studied. Stress-redistribution-reinjection involves imaging under stress, a delay of 3-4 hours to allow redistribution of the tracer, injection of another dose, and repeated imaging. The other approach is rest-redistribution. Thallium-201 is injected into the resting patient, imaged, and imaging again performed 3-24 hours later. Criteria for identifying viable segments vary and may be based on qualitative or quantitative analysis . Examples include increased uptake in redistribution or reinjection images, and uptake of 50% or more of the maximum in early, redistribution or reinjection images.

Most studies have involved the use of SPECT, which allows tomographic imaging with gamma cameras. In some studies, planar gamma camera imaging has been used.

Correlation studies with thallium-201

Some studies have compared thallium-201 with PET or DEC in the assessment of myocardial viability, without proceeding to measurement of recovery of function after revascularization. These studies are correlations rather than accuracy studies.

The proportion of segments classified as non-viable in the thallium study and classified as viable by FDG PET was 25% in the case of thallium-201 stress-redistribution-reinjection SPECT and 23% for thallium-201 rest-redistribution SPECT (27, 95). Panza et al. (74) found that 36% of segments classified as viable by thallium-201 SPECT were nonviable according to DEC.

Accuracy studies with thallium-201

A total of 24 papers on the accuracy of thallium-201 myocardial viability studies were identified. For three of these (38, 66, 71) which were included in an earlier review by Bax et al. (20), the data provided did not allow valid calculation of sensitivity and specificity. All the remaining 21 papers gave segment-based accuracy data. Three papers also gave patient-based data . The imaging technique was SPECT in 16, planar in three, both in one and unidentified in one. Eight of the studies used the stress-redistribution-reinjection approach and 13 the rest-redistribution method.

In the segment-based studies, viable dysfunctional segments were defined as those with improved function after revascularization. Echocardiography was most commonly used as the reference method, but radionuclide ventriculography and contrast ventricular angiography were also used. In the patient-based analyses, viability was defined as improvement in LVEF after revascularization.

For segment-based studies using the stress-redistribution-reinjection technique, sensitivities ranged from 72 to 100% and specificities from 38 to 98%. Only one of the eight papers reported sensitivity and specificity both above 70%. The remainder gave sensitivity values in the range 77-100% and specificities in the range 38-69%.

For segment-based studies using the rest-redistribution technique, sensitivities ranged from 70 to 100% and specificities from 22 to 92%. Six of 13 papers reported sensitivities and specificities both above 70%. For the remainder, sensitivity ranged from 70 to 100% and specificity from 22 to 65%.

All studies reporting both sensitivity and specificity equal to or greater than 70% were retrospective and did not involve consecutive patients. In contrast, only 25% of the PET, and 29% of the echocardiography segment-based accuracy studies, with sensitivity and specificity values of 70% or more, fell into this category. The results of the better quality studies indicate that while low false negative rates can be achieved in the detection of viable segments with thallium-201 imaging, false positive rates will be high.

The three studies which gave the results of patient-based accuracy analyses were prospective or had consecutive patients and seem to have been free of selection bias. Sensitivities ranged from 65 to 100% and specificities from 55 to 73%, but with wide confidence intervals.

Comparisons of the accuracy of thallium-201 imaging, PET and DEC

Twelve papers compared the accuracy of thallium-201 imaging and DEC in segment-based analyses of myocardial viability, in the same patients. Sensitivity for the echocardiography technique ranged from 68 to 95%, compared to 86 to 100% for the thallium-201 studies. Specificity for echocardiography ranged from 63 to 95%, compared to 22 to 98% for thallium-201. The sensitivity for thallium-201 was generally higher than that of echocardiography, while the specificity was substantially lower, except in one paper of poor quality. The differences ranged from -3 to 23 % for sensitivity and 20-47% for specificity.

Table 6 compares the sensitivity and specificity ranges for all PET, echocardiography and thallium-201 studies which were prospective or involved consecutive patients. While the sensitivity of thallium-201 imaging is comparable to that of PET and echocardiography, its specificity is lower, particularly in the segment-based studies. Thallium-201 imaging appears to be less accurate than PET or dobutamine echocardiography. While it can achieve comparable or higher sensitivity, specificity is lower, and false positive rates will be substantially higher than for the other techniques.

Table 6: Performance data from higher quality PET, DEC and thallium-201 studies*

Technique	Sensitivity, %	Specificity, %
Segment-based		
PET	75-95	67-84
Dobutamine echocardiography	68-97	62-95
Thallium-201 SPECT or planar	75-93	31-56
Patient-based		
PET (one paper only)	82	88
Dobutamine echocardiography	82-100	70-86
Thallium-201 imaging	65-100	55-73

*Prospective or retrospective with consecutive patients, free from selection bias.

Contribution of thallium-201 myocardial viability studies to patient management and outcome

Four papers were identified which examined outcomes for patients who had undergone thallium-201 myocardial viability studies. Only one study was prospective. In three studies SPECT was used and planar gamma camera imaging in the other. Results from the prospective study (34) suggest that the combination of conventional echocardiography and thallium-201 SPECT may

allow the accurate prediction of those patients who would be at high risk of death if medically treated, and who would benefit from revascularization. However, the number of medically treated patients was small, and confidence intervals for the results would be rather wide. The retrospective studies suggest that thallium studies may have had a useful predictive value, but their reliability is uncertain. Further studies are needed in this area.

FDG SPECT imaging for assessment of myocardial viability

Method

In general, FDG SPECT studies conducted to assess myocardial viability have been performed with rotating dual- or triple-head gamma camera systems. To enhance FDG uptake and to obtain good image quality, studies were performed after oral glucose loading or after the insulin clamp procedure (15, 16, 18, 19, 49, 51, 85, 91).

FDG SPECT is an evolving technique. One of the most recent developments is the use of dual-isotope simultaneous acquisition (DISA) of perfusion and metabolism images. It has been suggested that DISA SPECT can shorten image acquisition time and easily detect areas of perfusion-metabolism mismatch.

Several investigators have developed protocols for using a Tc-99m-labeled agent (sestamibi or tetrofosmin) as a perfusion tracer and FDG as a metabolism tracer followed by DISA SPECT to identify both cardiac ischemia and hibernating myocardium in patients with LVD (16, 17, 18, 58, 78, 79, 81, 82, 100). They reported promising results suggesting that the dual-isotope approach for FDG SPECT imaging is feasible. These findings warrant further investigation, in larger, well-designed studies.

FDG SPECT has been suggested as a lower-cost, more readily available alternative to PET (27, 81, 85). However, the coincidence detection systems and 511keV collimators used with SPECT to image FDG do not produce the same image quality as PET scanners and longer acquisition time is required (14, 27, 32, 49, 51, 54, 81).

The use of FDG SPECT imaging for MV assessment in combination with cardiac perfusion agents is technically demanding in terms of both equipment and interpretation (17, 51, 81, 82).

Correlation studies

Correlation studies have compared the use of FDG SPECT (analyzed visually or semi-quantitatively) and FDG PET (using quantitative analysis) for MV assessment. Overall agreement between the two techniques in the differentiation between viable and non-viable myocardium ranged from 76% to 94% (15, 16, 17, 19, 54, 60).

Despite good overall agreement, discordance has been reported, especially in myocardial regions where there is severe LVD. The differences varied depending on the severity of LVD and the type of data analysis (segment-based vs. patient-based). Details of studies that were reviewed for the assessment are shown in Table 7.

Table 7: Primary correlation studies on FDG SPECT

Study	Patients	Results
Burt et al. 1994 (27) *prospective	*20 consecutive patients with known/suspected previous MI; significant fixed defects on reinjection rest Tl-201 SPECT	*FDG PET: 14/60 segments (7/20 patients) "probably viable" *FDG SPECT: 13/60 segments (8/20 patients) "probably viable"
Cornel et al. 1997 (34) *prospective	*20 patients with prev. MI (mean LVEF 39% ± 16%, in 12/20 pts: 35% or less)	*overall PET/SPECT agreement of 76% (segments-based) *comparable results in 17/20 patients
Calhoun et al. 1996 (28) *retrospective observational study	*59 consecutive patients (CAD and LVD; FDG SPECT), grouped into: SS evidence of MV vs. without MV in areas of depressed flow (mean LVEF 21% ± 7%).	*34/59 patients (58%) with MV on FDG SPECT (29/34 patients had subsequent revasc). *30-day survival for all: 86%
Chen et al.. 1997 (32) *prospective	*36 randomly selected patients (referred for PET MV assessment)	FDG SPECT (HE collimator): 88% concordance with FDG PET; moderate agreement; Se 61%; Sp 91% (v FDG PET) FDG SPECT (dedicated 511 keV collimator): 90% concordance with FDG PET; excellent agreement; Se 86%; Sp 91% (v FDG PET)
Srinivasan et al. 1997 (91) *prospective	*28 patients with CAD; 18 prior MI; impaired LV function or a RWM abnormality) *mean LVEF 33% ± 13%.	SPECT vs. PET: good agreement, 94% concordance for 50% FDG threshold value Tl-201 SPECT vs. FDG PET/SPECT: for 50% threshold: concordance in 90% (SPECT) and in 92% (PET); concordance in 88% (SPECT) & in 90% (PET) in 777segs Scarred segments by Tl-201: 59/137 (43%) viable by FDG PET; 52/59 (88%) also viable by FDG SPECT

Accuracy studies

Details of studies on accuracy of FDG SPECT imaging for MV assessment which met the selection criteria used for the literature review are summarized in Table 8.

The reported results showed that FDG/myocardial perfusion SPECT, FDG/myocardial perfusion PET, stress-reinjection Tl-201 SPECT, rest-redistribution Tl-201 SPECT and dobutamine echocardiography had a

comparable sensitivity to assess improvement of regional function. However, specificity differed between the techniques. Further details of these studies, giving performance data for different types of cases, are included in Volume 2.

These studies took a variety of approaches and comparison between them is not straightforward. None clearly met all the criteria for the methodological quality formulated in Appendix A. Areas of methodological weakness included study design, selection of patients, matching of studied patients to the target population, blinding of the interpreters of tests, and post-test selection bias. The studies have included patients scheduled for revascularization based on clinical, angiographic and echographic data. Most of the analyses included only dyssynergic segments successfully or adequately revascularized. Information on patients lost to follow-up is rare.

Table 8: Results of studies on overall performance of FDG SPECT in MV assessment

Paper	Sensitivity	Specificity	Predictive values
Bax et al., 1997 (11) n=27	87% (overall, segment-based)	78% (overall, segment-based)	PPV 72%; NPV 90% (overall, segment-based)
Cornel et al, 1997 (34) n=30	84% (overall, segment-based) 93% (overall, patient-based)	86% (overall, segment-based) 87% (overall, patient-based)	PPV 78%; NPV 90% (overall, segment-based)
Bax et al. 1996 (13) n=17	89% (overall, segment-based) 83% (overall, patient-based)	77% (overall, segment-based) 100% (overall, patient-based)	PPV 62%; NPV 94% (overall, segment-based)
Bax et al. 1997 (10) n=24	89% (overall, segment-based)	81% (overall, segment-based)	
Bax et al. 1997 (12) n=55	85% (overall, segment-based)	75% (overall, segment-based)	PPV 63%; NPV 91% (overall, segment-based)

Similar data have been reported in a further study by Bax et al. (9) who prospectively evaluated the role of FDG SPECT in the prediction of improvement in contractile function after revascularization. They included 41 patients with wall motion abnormalities on resting echocardiography scheduled for revascularization who underwent rest Tl-201/FDG SPECT. At a cutoff value of 6% (FDG vs. Tl-201 activity) a sensitivity of 81% and a specificity of 87% were reported. The authors concluded that these results demonstrated that "FDG SPECT can detect recovery after revascularization".

Calhoun et al. (28) reviewed the findings from FDG/myocardial perfusion SPECT imaging studies and treatment outcomes in 59 consecutive patients with

angiographic evidence of CAD and depressed LVF. Clinical decisions based on FDG SPECT scans were obtained from chart review.

Thirty-four patients (58%) had evidence of hibernating myocardium on FDG SPECT and 29 of these subsequently had revascularization. Thirty-day survival for all revacsularized patients was 86%. The authors concluded that MV assessment with FDG SPECT imaging in patients with ischemic LVD led to a clinical decision for revascularization in "approximately half the patients with severe coronary disease and left ventricular dysfunction who were evaluated for myocardial viability".

Appraisal of the reviewed primary studies

The published primary studies are methodologically weak and tend to overestimate the diagnostic accuracy and value of FDG SPECT. More details on the methodological quality of the reviewed studies are included in volume 2 of this report.

Currently, there are no published randomized controlled trials conducted to evaluate the diagnostic accuracy and impact of the use of FDG SPECT alone, or in combination with perfusion imaging for pre-revascularization MV assessment in patients with chronic CAD and severely impaired LV function.

No reports were located on studies comparing outcomes of patients with or without viable myocardium on FDG SPECT, who were followed-up with or without revascularization were located.

Cardiac FDG SPECT imaging appears a promising technique that may allow cardiac FDG imaging in centres without PET equipment. The feasibility of imaging FDG uptake with SPECT has been demonstrated but the quality of the available evidence is limited in some respects and does not allow an adequate evaluation of its potential role in routine clinical practice.

Currently, few data are available on whether FDG SPECT can predict improvement in regional and global LV function after revascularization in these patients and outcomes data are lacking.

SPECT imaging with technetium labeled agents for assessment of myocardial viability

Background

SPECT is the nuclear medicine technique most frequently used for MV assessment. The most commonly used radiopharmaceutical is Tl-201. However, its low radiation energy is suboptimal for gamma camera imaging and its long half-life limits the injected dose, which may further reduce the image quality.

Technetium-99m (Tc-99m) labeled agents have emerged as alternatives to Tl-201 for imaging of regional myocardial perfusion Technetium has better physical and kinetic properties for gamma camera imaging and gives improved image quality. Its short half-life allows a higher injected dose compared to Tl-201, resulting in higher count rates.

Available evidence on Tc-99m imaging

There is a lack of adequate information on the use of Tc-99m-labeled agents for MV assessment in patients with chronic CAD and LVD (1). Findings from recent reviews of the literature are summarised in Volume 2 of this report. Some key points are as follows.

Tc-99m sestamibi

Tc-99m-sestamibi (sestamibi) is the most commonly used Tc-99m labeled agent in cardiac SPECT imaging.

Several studies have shown the validity of sestamibi as a marker of MV when administered during evolving ischemic injury in the setting of myocardial stunning (29, 45, 46). However, it may result in overestimation of scarred myocardium, when compared to Tl-201 scintigraphy or FDG PET.

The underestimation of MV with sestamibi imaging has been reported by several studies conducted in patients with chronic CAD and LVD, in which sestamibi imaging was compared to Tl-201 imaging and/or FDG PET (17, 29, 45, 46).

Some of the studies comparing rest-redistribution Tl-201 imaging with sestamibi imaging were consistent in showing that sestamibi imaging is less accurate in MV detection and overestimates perfusion defects in approximately 25% of myocardial regions in patients with CAD (17, 20, 29, 46, 78, 80).

Approximately 50% of the myocardial segments with moderate or severe reduction in sestamibi uptake (indicating non-viable myocardium) were shown to be viable by FDG PET (17, 29, 31, 45, 80).

Studies comparing sestamibi imaging with improvement of contractile function after revascularization reported sensitivities of 73 - 100%, and specificity values between 35% and 86% (17, 20, 29, 45).

New developments

Several approaches have been advocated to improve the diagnostic accuracy of sestamibi imaging for MV assessment. They include stress-rest imaging, ECG-gated SPECT, quantitative analysis, delayed imaging after tracer administration, tissue attenuation correction methods, and administration of nitrate before sestamibi injection.

Franken et al. (40), pooled data from 3 studies (51 patients, 166 segments) and found that results obtained with sestamibi compare favorably with those for Tl-201, with a PPV of 89%, a NPV of 82%, and an overall accuracy of 85% for functional improvement after revascularization. However, caution is warranted on these values because functional follow-up was reported in a small number of patients.

Conflicting results have been obtained with respect to the value of quantitative sestamibi imaging (29, 45, 78). Many studies have not used an independent reference standard and have compared the two tracers with identical arbitrary cut off values optimized for Tl-201 (29, 78).

Reviews of research on the use of sestamibi imaging for MV assessment in patients with chronic CAD and LVD conclude that its role for this indication remains controversial (17, 20, 22, 29, 31, 45, 46, 63, 64, 78, 81). The majority of clinical studies reported on the tendency of sestamibi imaging to underestimate the extent of MV in patients with chronic CAD and LVD when FDG PET and post-revascularization functional recovery are used as standards of reference. Better quality studies are needed to determine the role of sestamibi imaging for MV assessment.

Other Tc-99m labeled agents

Recently, other Tc-99m labeled myocardial perfusion agents such as teboroxime, tetrofosmin, furifosmin and Tc-99m-N-NOET have been developed and are currently under investigation (17, 29, 45, 63, 64).

Conclusions

The potential role of SPECT imaging with Tc-99m-labeled agents for MV assessment in patients with chronic CAD and LVD is not yet determined. The value of sestamibi SPECT imaging remains a controversial issue at present. Evidence on the use of other Tc-99m-labeled agents for this indication is very limited.

Magnetic resonance imaging in assessment of MV

Both magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) offer potential as methods for investigation of viability. The following discussion covers their application to assessment of MV in different clinical situations. A number of reviews have outlined their possible strengths and areas of application (26, 31, 101, 103). While these techniques have been used in the study of cardiac disease for many years, their application to evaluation of myocardial viability has so far been quite limited. The available literature suggests that this may be an emerging field of use.

Van der Wall et al. (101) note that three standards for myocardial viability can be used for the prospective identification of jeopardized but viable myocardium for purposes of guiding therapeutic interventions in individual patients. These are preserved coronary flow (adequate perfusion); preserved wall motion (systolic wall thickening): and preserved metabolism (metabolic integrity). MR techniques have a great potential to measure all three standards. Adequate perfusion can be assessed by spin-echo MRI and/or ultrafast MRI, systolic wall thickening by cine MRI and the presence of metabolic integrity can be determined by MRS.

Magnetic resonance imaging

Studies on performance and feasibility

Dendale et al. (36) studied the relation between two MRI approaches: demonstration of wall motion recovery using dobutamine and measurement of perfusion patterns. Twenty-eight patients who had had AMI were studied prospectively. There was strong correlation between contrast MRI findings and response to low dose dobutamine stimulation. The authors suggest, on the basis of high PPV values for negative contrast MRI or subendocardial infarct enhancement, that dobutamine studies would not be needed for that group of patients. Numbers in the subgroups were small. There was no follow-up observations of wall motion and the practicalities of basing decisions on a PPV of close to 80% would need to be considered.

Geskin et al. (42) in a study with 20 patients, were able to demonstrate the feasibility of quantifying response of intramyocardial function to low dose dobutamine. The feasibility of functional MRI in assessing changes in tissue perfusion has also been explored.

Correlation studies

A correlation study with thallium-201 was used by Lawson et al. (55) to study the utility of wall thickness measurements for assessment of scarred myocardium.

Twenty-four patients were studied, 17 with previous AMI (> 4 months) and seven who were admitted with AMI and had early imaging.

Gradient echo cine MRI was performed using a 1.5T scanner and redistribution thallium-201 imaging with SPECT. Thallium uptake was correlated with MRI-measured wall thickness at end-diastole and end-systole for 18 segments for each ventricle. End-systolic was a better diagnostic parameter than end-diastolic wall thickness (ROC analysis), correlating with normalized thallium uptake in 16 of 18 segments, compared to 4 of 18 for end-diastolic.

Two correlation studies compared technetium - 99m - MIBI SPECT (2) and technetium - 99m - tetrofosmin SPECT (92) with MRI. The emphasis in both was on validation of the nuclear medicine technique, with MRI being used as the gold standard. There was, overall, good correlation between gated SPECT and MRI in measurement of ejection fraction, of wall motion and of wall thickness. However, in segments with reduced perfusion, agreement was poorer.

Yang and colleagues (108) have reported results of an early clinical trial of a cardiac MRI system, in which comparison was made with echocardiography in evaluation of LVF in 85 patients. Two independent observers scored wall motion and image quality using a 16-segment model and rank order analysis. There was no significant difference between the two imaging methods for patients who had acceptable echocardiography image quality. For those with sub-optimal echocardiography image quality, MRI provided adequate visualisation in a significantly higher proportion of cases. The authors suggest the new MRI system provides clinically reliable evaluation of LVF and complements suboptimal echocardiography.

Studies of accuracy and predictive value

Dendale et al. (36) compared dobutamine MRI with two dimensional echocardiography in 37 patients with recent AMI. Of 46 consecutive patients < 80 years old who were eligible for the study, five had poor quality MRI images and another four were excluded because of echocardiographic image degradation. Follow-up echocardiography was available for 24 patients at three to six months.

Results for improvement in function after stimulation with dobutamine were not statistically different for the two imaging methods, but subgroup analysis indicated that seven cases (30%) were classified differently by the two techniques.

For the group of 24 patients who were followed up, original imaging findings were compared to indications of improvement in wall motion. For MRI, sensitivity and specificity were 91% and 82% respectively, compared to 82% and 85% for echocardiography. Differences in this small series were not statistically significant.

Baer and colleagues (5) published two correlation/accuracy studies. In the first of these dobutamine MRI was compared to FDG PET in 35 consecutive patients with AMI with an infarct age of > 4 months. Three patients were excluded from final evaluation (MRI motion artifacts in two, diminished PET image quality in the other). Multiple views of each coronary artery were obtained using angiography. Two definitions of viability as assessed by MRI were used - end-diastolic wall thickness of ≥ 5.5mm and evidence of dobutamine-induced systolic wall thickening of ≥ 1mm.

Diagnostic agreement between FDG uptake and myocardial morphology was 83% and between dobutamine-induced contraction reverse and FDG PET was 89%.

Comparison of segmental MRI (2,200 segments included) and FDG PET gave the following results for prediction of residual metabolic activity:

	Dobutamine-induced wall thickening	End-diastolic wall thickness	Viable if at least one MRI parameter met criteria
Sensitivity	81%	72%	88%
Specificity	95%	89%	87%

The authors suggest taking both parameters into account to maximize the sensitivity of MRI in detection of viable regions.

In the second study (8), dobutamine MRI and dobutamine transesophageal echocardiography were used in imaging 43 consecutive patients who had had AMI (infarct age ≥ 4 months). FDG PET was used as the reference standard. The infarct region was considered viable if a dobutamine contraction reserve could be assessed visually by echocardiography or quantitatively by MRI in ≥ 50% of segments graded as akinetic at rest. With FDG PET - defined myocardial viability as the standard, sensitivity and specificity of DEC were 77% and 94% compared to 81% and 100% for dobutamine MRI. MRI therefore had rather better performance.

Baer et al. (8) suggest that although MRI provides an easily reproducible and complete study of the entire left ventricle, there are some important factors that make echocardiography the more attractive imaging technique for the assessment of myocardial viability.

Standard MRI techniques do not allow real time imaging; the quantitative assessment of systolic wall thickening is time consuming; echocardiography is widely available, can be performed at the bedside and there is widespread diagnostic experience with its use.

On the other hand, transesophageal echocardiography is more invasive than MRI and many patients find it unpleasant. They suggest that future availability

of faster MRI techniques with semiautomated assessment may facilitate the clinical use of MRI in this application.

A recent paper by Nagel et al. (68), which considered a group of individuals with suspected coronary artery disease, compared DEC with dobutamine MRI in 208 consecutive patients. They used identical stress protocols for DEC and MRI studies. Eighteen patients could not be examined by MRI (because they were claustrophobic, obese or had retro-orbital metal). A further 18 patients could not be examined by DEC because of poor image quality. Sensitivity and specificity of dobutamine MRI were 82.6% and 85.7% compared to 74.3% and 69.8% for DEC.

A further study by Baer and colleagues (6) considered the predictive value of dobutamine MRI for recovery of dysfunctional myocardium after successful revascularisation. A series of 43 patients from 122 consecutive cases was evaluated. They had all been successfully treated. Dobutamine MRI and angiography results before revascularisation were compared with those of angiography and rest MRI four to six months after the procedure. Dobutamine-induced systolic wall thickening (SWT) had a sensitivity of 89% and specificity of 94% in predicting LV functional recovery, compared with corresponding values of 92% and 56% for preserved end-diastolic wall thickness (DWT). Segments which remained akinetic after revasularisation had significantly lower DWT than those with improved SWT. The authors conclude that MRI is a highly accurate predictor of LV functional recovery and that the presence of significantly reduced DWT reliably indicates irreversible myocardial damage.

A study by Klow et al. (52) on a small series indicated that cine MRI provided additional information to angiography and had a useful predictive performance. Seventeen patients with previous AMI, angina and LVD were studied prior to surgery and at an average of 22 months after revascularisation. Improvement in SWT was seen in 65% of segments that had a DWT of > 15mm before surgery. Only 4% of segments with a DWT of < 6mm improved. MRI was unable to predict functional outcome with wall thickness in the range 6 - 15mm.

In another small series (17 patients referred for coronary vascularisation) studied by Sayad et al. (83) dobutamine MRI with myocardial tagging had a sensitivity of 89% and specificity of 93%. Segments with end SWT of < 7mm at rest did not demonstrate contractile reserve or improve on revascularisation.

Comments on the reviewed literature

The limited information from the reviewed literature suggests that MRI has considerable promise as a method for assessing myocardial viability. The available studies have a number of limitations, some of which are discussed by the authors, but there is useful evidence that MRI compares favorably with other FDI techniques in terms of accuracy and predictive ability.

Use of MRI methods in this application is still at an early stage. Further studies will be required to establish its status in this area of diagnostic imaging, and will need to take account of the continuing development of the technology, including the evolution of functional MRI methods.

Magnetic resonance spectroscopy

Only feasibility studies of the application of MRS to assessment of myocardial viability were located. These include the study by Bottomley & Weiss (25) on the measurement of creatinine in infarcted myocardium. In a recent review of cardiac MR imaging, Smith (90) comments that despite numerous scientific efforts, MRS of the heart has not yet become a routine clinical examination. Limitations have included difficulties in precise quantification of metabolites in the beating heart, a lack of specificity of the metabolic changes found in important cardiac diseases and spatial localisation of a region of the myocardium. To obtain an adequate signal to noise ratio, clinical studies are performed with surface coils, which limit the investigation of regional myocardial metabolism to the anterior wall of the heart. Measurements of global myocardial metabolism are usually contaminated by signal from the anterior chest wall and from blood in the cardiac chambers.

At this stage, MRS in the assessment of MV appears to still be in the research domain.

The clinical context of FDI for assessment of myocardial viability

The pertinent clinical observations that have led to the use of FDI in this application were that some areas of apparently irreversible myocardial damage recovered following revascularisation; that some patients with severe damage (ischemic cardiomyopathy) showed some recovery of LVF with clinical improvement; and that there was a small group of patients whose primary clinical problem was heart failure, with little or no angina, who responded favourably to revascularisation. The advent of FDI techniques gave hope that this last category of patients might be more accurately selected.

McDonald (personal communication) suggests that, while useful information has emerged on recovery of the myocardium after prolonged impairment and the accuracy of FDI methods, several questions remain unanswered. These include the extent to which revascularisation can improve heart failure, quality of life and survival in patients with extensive ischemic left ventricular impairment; how common such patients are in routine practice; and to what extent the various imaging tests can aid in predicting a worthwhile response from the patient's point of view. Patients who have chest pain as the primary problem but who also have hibernating myocardium present a different clinical situation.

Clinical issues and studies of FDI methods

The following notes have been prepared with particular reference to FDG SPECT, but appear to be applicable to all the FDI methods considered in this report. Some general points are that:

- Most studies have based their analysis on regional functional outcome rather than on global functional outcome.
- Segmental analysis is statistically relevant but may not be clinically relevant.
- When patient-based analysis was used, different measures of substantial viability were used for global function recovery.
- Not all studies have stated clearly the degree of anticipated improvement of LVF.

Recently, several investigators have commented on the unresolved clinical issues associated with the pre-revascularization MV assessment and suggested that some are likely to affect the diagnostic accuracy of cardiac imaging techniques and their potential role in the routine clinical practice (17, 22, 24, 47, 48, 50, 84).

Definitions

One of these issues is the definition of viable myocardium. Viable myocardium may be normal, hibernating or stunned (both characterized as reversibly

dysfunctional myocardium) while non-viable myocardium represents scarred myocardium (infarcted/necrosed myocardium).

The terms viability and potential reversibility are used synonymously in many papers (50) although the pre-revascularization MV assessment is most clinically relevant in patients with chronic impaired LV function, for detection of hibernating myocardium (84). Hibernating myocardium is viable, but viable myocardium is not necessarily hibernating. The distinction is important since various cardiac imaging modalities use different markers for MV (47, 77, 78). However, the clarity with which chronic impaired LV function can be defined as hibernation, repetitive stunning or a combination of the two is still limited (24, 47). Also, the exact mechanism of hibernation remains elusive (31, 61).

Quantification of viability

Quantification of viable myocardium has been identified as another clinical issue that is likely to influence the reliability of different cardiac imaging techniques (47, 50, 61). A given myocardial region may not be entirely scarred or entirely hibernating and the detection of viable myocardium is not in itself an indication for revascularization (47, 48). In some patients there could be some myocardial regions which include normal, infarcted, stunned and hibernating "micro regions".

Several investigators suggested that the relative proportion of hibernating myocardium to other abnormalities in a given segment and the total extent of hibernation in the LV myocardium will determine the extent of recovery of regional and global LV function after revascularization (17, 22, 47, 48, 61). It has been estimated that at least 20% of the myocardial region should be reversibly dysfunctional before an improvement in ejection fraction (EF) can be expected (48, 61). The "substantial viability", used as a measure of the patient's ability to recover functionally after revascularization, has been defined differently in the reviewed literature (12, 13, 17, 28, 34).

Patient selection

Another issue is that the specific category of patients most likely to benefit from MV assessment is not fully delineated (17, 24, 61). It has been suggested that patients with severely impaired LVF who have no disabling angina pectoris (which alone may guide therapy) but have congestive heart failure are most likely to benefit from MV assessment (17, 47, 48, 61, 78). It has also been suggested that results of MV assessment are clinically most relevant in patients with severe global LVD and in myocardial regions with resting wall motion abnormalities (86).

Schoeder et al. (86) consider that detection of MV is important in the small subgroup of patients with akinesia or severe hypokinesia, significant stenosis in the related coronary arteries, and severe reduced uptake of Tl-201 or sestamibi during scintigraphy. According to Beller (22), accurate MV detection allows for

selection of patients with CAD and resting LVD, characterized by severely depressed LVEF (not defined), "who will most benefit from revascularization". There is limited information regarding the application of revascularization techniques in patients with more severe LVD (31, 48). In the reviewed literature, the severity of LVD is defined by different values of LVEF, ranging from <20% to ≤40% (17, 48, 99).

It is believed that MV assessment is not relevant in patients with mild LVD (17, 48, 78). However, most of the patients included in the published primary studies on the use of FDG SPECT imaging for MV assessment have mild-to-moderate impaired LV function. The selection bias may explain the comparable accuracy of the various cardiac imaging techniques in predicting recovery of function after revascularization (47, 48). It has been suggested that as LVD becomes more severe it is possible that the accuracy data will differ more (47). The results reported by the reviewed primary studies suggest that severity of LVD is an important factor that is likely to alter the diagnostic accuracy of imaging techniques. McDonald (personal communication) suggests that there is every reason to believe that imaging accuracy will be less for those patients who are of interest for this FDI application.

Follow up after revascularisation

The optimal time for follow-up after revascularization has yet to be determined (20, 47). The reviewed accuracy studies provide follow-up data at three months. It has been suggested that, in some patients, recovery may occur at 6-12 months after revascularization. However, longer follow-up may be associated with restenosis or graft occlusion and it may be important to have serial measurements after the procedure (19, 20, 24, 47, 48).

Among the questions frequently raised on the topic of MV assessment is that of which endpoints should be used to determine the outcome after revascularization. Although improvement in wall motion abnormality or EF may be important from a scientific point of view (objective and reliable endpoints), from the clinical (and patient's) point of view improvement in symptoms and survival are more important.

The standard used in most of the reviewed studies is the echographic determination of improved wall motion (which suggests improvement of regional dysfunction). However, it has been argued that wall motion may have limited significance in terms of improvement in EF, symptoms and survival (47, 48, 61, 99). Some investigators have suggested that the primary endpoint should be improvement in EF (which suggests recovery in global function) (16, 17, 47, 48, 61). Some investigators have suggested that the best primary endpoint is the improvement in EF (which suggest recovery in global function) and secondary endpoints should be improvement in symptoms and survival. It has also been argued that recovery of the regional LVF after revascularization of viable but

dysfunctional myocardium may not be the only, or even the most important endpoint (23, 24, 78).

Effects on outcomes

Assessment of the extent of MV may help to select patients who may benefit from revascularization. However, following such selection, many other factors will affect recovery of LVF after revascularization including the coronary anatomy, presence/absence of peri-operative myocardial infarction, completeness of revascularization, and graft patency (11, 17, 19, 47, 48, 86).

Discussion

The diagnostic imaging technologies considered in this assessment have the potential to improve the management of patients with dysfunctional myocardium with symptoms of heart failure. The additional information available through functional diagnostic imaging should improve the quality of decisions on which treatments should be offered to individual patients. These imaging studies could be expected to have a beneficial effect on health outcomes and to lead to efficiencies through avoidance of inappropriate procedures in patients who would not benefit from revascularisation.

However, review of the available literature suggests that the place of these imaging technologies in routine health care is still uncertain. It is difficult both to make valid comparisons between individual imaging methods and to judge how each of these might be used routinely and to what effect. The existing studies can yield no more than some tentative conclusions.

As this report has discussed in detail, there are substantial methodological limitations in most of the studies that are reported in the literature. There are relatively few good quality data on the accuracy of imaging methods in the routine situation and even fewer on their influence on patient management decisions. Equipment and software for FDI technologies continue to evolve, so that some of the reported studies may soon become less relevant for informing discussion about the future of FDI in the assessment of myocardial viability.

The information that is available tends to reflect the efficacy rather than the effectiveness of the imaging methods. The accuracy of the FDI technologies may be poorer in those patients who are of particular interest, those with heart failure, - than is indicated by the literature. Those patients with severe LVD are more likely to have mixtures of surviving myocardium, some normal, some subjected to abnormal stresses, stunned myocardium and a spectrum of structural damage currently classified as 'hibernating myocardium'. This is likely to lead to inhomogeneity of response to testing and to revascularisation and could amplify differences between methods (McDonald, personal communication).

Several practical issues need to be borne in mind when considering their possible routine application throughout a health care system. These are complex imaging procedures. Excellent training and quality assurance protocols would need to be in place in those institutions using such methods. Individual FDI technologies would not necessarily be applicable to all patients who might benefit from the additional information produced. In the studies reviewed here, it was notable that in many cases there were significant numbers of uncompleted or non - feasible imaging exams because of poor image quality and other technical difficulties.

Comparison of the different methods is difficult. There is evidence of useful performance for PET, DEC, and SPECT - based methods. For accuracy, in terms of identifying viable regions of the myocardium, PET and DEC seem to offer similar levels of performance. However, the opinion reached in this assessment is that, given the quality of the studies, there is limited evidence of accuracy of these methods in this application.

There is some evidence that Tl-201 SPECT could have higher sensitivity but lower specificity than PET. Studies which found higher specificities for Tl-201 SPECT were of poorer quality, being retrospective and having non-consecutive series.

FDG SPECT appears to have comparable sensitivity to PET and DEC, but the studies undertaken so far are methodologically weak and tend to overestimate its accuracy. Sestamibi SPECT appears to be less accurate than PET or Tl-201 SPECT.

There is still limited evidence on MRI methods, but there are indications that these may become more important in the future. MRI appears to have considerable promise in this application.

There is little information on the contribution of these FDI methods to patient outcomes. There is some evidence that PET is able to predict outcomes, but this is not conclusive. The evidence for the predictive value of DEC is very limited.

Outcomes studies suggest that Tl-201 SPECT may have a useful predictive value, but their reliability is uncertain. The feasibility of imaging FDG uptake with SPECT has been demonstrated but the quality of the available evidence does not allow an adequate evaluation of its potential role in routine clinical practice. The potential role of SPECT imaging with Tc-99m-labeled agents is not yet determined.

A major issue is that there is limited evidence for improvements in outcome after revascularization for patients who have been selected for such intervention on the basis of imaging examinations. There is a need for high quality prospective studies with a large numbers of subjects in both the target and control groups, and with adequate follow up times. There could be merit in putting in place multicentre studies to increase patient numbers.

McDonald (personal communication) considers that essential features of a high quality study on the performance and value of FDI methods in this application would include:

- posing the clear relevant clinical *question* (value of revascularisation in patients with severe heart failure);
- consecutive *recruitment* of patients with eligibility requirements based upon clinical relevance and patient preference rather than only considerations of sample size or administrative convenience;

- detailed *clinical description* based upon all relevant attributes including comorbidity, clinical severity, disease stage, treatment response and social class, documentation of treatment and changes;
- *comprehensive protocol* including formal definitions of chest pain and breathlessness;
- primary *outcome measurement* of survival, quality of life and patient satisfaction and secondary outcomes - relevant adverse events, functional exercise status, LVF and recovery of segments;
- *documentation of all patients* considered for inclusion, follow-up of all patients included; and
- *blinded reading* of images, testing of interobserver agreement.

Ideally, such a study might address efficacy of the FDI methods for assessment of MV through a large, multicentre randomized trial. In practice, this may well be too demanding to put in place. Perhaps a more practical approach for health systems to consider is demonstration of effectiveness using a data-base cohort analytic study of appropriateness of use and outcome. This could include appraisal of alternative imaging approaches.

The results of this assessment suggest that health professionals and policy makers should approach these FDI techniques for assessment of MV with some caution. Their promise is not yet matched by convincing evidence of benefit to health care, data on comparative performance are limited and technical development continues to be rapid. Cost issues (not considered here) could be important in decisions on use of these methods. Cost effectiveness studies would be valuable.

It is suggested that any use in Alberta of these methods for assessment of myocardial viability should be associated with prospective studies involving long term follow up of patients.

Appendix A: Methodology

A literature search for articles published between 1993 and November 1998, which reported studies on human subjects, was conducted. Sources of information included the following electronic databases: EMBASE, MEDLINE, ECRI's database. The literature search was kept updated during the review.

The words 'coronary disease', 'coronary artery disease', 'ventricular dysfunction, left', 'diagnostic imaging', 'positron emission tomography', 'tomography, emission-computed', 'nuclear magnetic resonance', 'magnetic resonance imaging', were used as subject headings.

The text words and phrases such as 'myocardial', "myocardial infarction', viability or viable', 'myocardial viability', 'functional', 'functional imaging', 'positron emission tomography', 'PET', 'MRI', 'magnetic resonance spectroscopy', 'MRS', 'dobutamine', 'echocardiography', 'dobutamine echocardiography', 'SPECT', 'fluorine-18-fluorodeoxy glucoze', '11C-acetate', 'carbon-11-acetate', 'technetium', 'thallium', 'cost$', 'economic$', 'economic aspect', 'costs and cost analysis' were used alone or in combination to ensure a high recall rate of the relevant references.

For each of the citations considered, the abstract was read (where available) and articles were excluded if they were outside the scope of the analysis. From the references identified, a selection was made and full articles that met the following criteria were retrieved:

- articles reporting results of prospective *and retrospective* studies (with series larger than 10 subjects) in which the diagnostic accuracy and validity of each of the selected FDI techniques was evaluated in patients with chronic coronary artery disease and LV dysfunction who are potential candidates for revascularization; only articles that contained accuracy data (sensitivity, specificity, positive and negative predictive values) or sufficient details so that accuracy data could be calculated;
- articles reporting results of studies that compared the functional outcome of individuals with and without viable myocardium on each of the selected FDI technique who were followed-up with or without revascularization;
- articles containing background information about selected FDI techniques.

Studies in patients with acute ischemic syndromes were excluded.

Editorials, letters, case reports and technical reports were excluded unless they provided information on clinical issues associated with MV assessment, characteristics of the selected FDI techniques, their cost, advantages and limitations, that was not available elsewhere.

The reference lists of the reports obtained through these searches were screened for additional articles.

Methodological quality of the primary studies included in the review was considered in terms of the criteria covering study design, study population, characteristics of the assessed FDI technique, determination of diagnostic accuracy and validity, and influence on management and outcomes. These criteria were formulated having regard to the information needed to confidently evaluate the relative merits of the selected FDI techniques for prediction of recovery of LV function after revascularization, in order to define their place in routine use.

The following were the criteria used for the appraisal of the accuracy studies included in the review:

Study design: study prospective or if retrospective patient selection blind to results

Description of study population: consecutive patients selected or valid justification provided for selection method; subjects adequately described, match target population; inclusion, exclusion criteria adequately described.

Characteristics of the assessed FDI technique: test method, criteria for detecting viability adequately described; reproducibility of results, inter-observer variability described.

Determination of diagnostic accuracy and validity: well defined reference method, adequately described; interpreters of any viability test blinded to the results of the other tests; evidence that selection for revascularization not influenced by the assessed viability tests; evidence that revascularization procedure not affected by test results; supporting data for accuracy measures reported; statistics on analytical performance reported with tests for statistical significance or confidence intervals.

For the appraisal of the outcome studies included in the review, the following criteria were used:

Study design: groups assigned to different treatments are matched or any differences evaluated in a valid statistical analysis.; study prospective or if retrospective , selection of patients blinded to outcomes.

Description of study population: consecutive subjects selected or valid justification of selection method provided; subjects adequately described; inclusion and exclusion criteria adequately described; study population matches target population; sample size adequate for statistically significant results.

Characteristics of the assessed FDI technique: test method, criteria for detecting viability adequately described.

Follow-up and outcome analysis: follow-up reported of treated and untreated subjects, including those in whom the assessed method did not provide diagnostic information; all patients deceased or lost to follow-up reported or

dealt with in statistical analysis; follow-up period range and mean given including period from revascularization; follow-up period long enough for meaningful results; details of treatments given; evidence that selection for treatment not influenced by test; outcome assessment blind to diagnostic data; clear specification of clinically relevant outcome measures; valid statistical analysis of outcome data.

In this report:

Efficacy refers to the performance of a technology under 'ideal' conditions or conditions of best practice; and

Effectiveness refers to the performance of a technology under 'routine' conditions, for example when it has become widely distributed in a health care system.

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